



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,887	12/11/2001	Geoffrey W. Krissansen	8654/2072	2382
29933	7590	01/16/2007		
PALMER & DODGE, LLP KATHLEEN M. WILLIAMS 111 HUNTINGTON AVENUE BOSTON, MA 02199			EXAMINER YAO, LEI	
			ART UNIT	PAPER NUMBER
			1642	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/16/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/014,887

Applicant(s)

KRISSANSEN ET AL.

Examiner

Lei Yao, Ph.D.

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7, 10-15, 18-23, 26-31, 34-39, 42-47 is/are pending in the application.
- 4a) Of the above claim(s) 10-11, 15, 18, 19, 23, 26, 27, 31, 34, 35, 39, 42, 43, 47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-4, 7, 12-14, 20-22, 28-30, 36-38 and 44-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Response to Arguments and Amendment

The Amendment filed on 11/22/06 in response to the previous Non-Final Office Action (8/23/06) is acknowledged and has been entered.

Claims 5, 6, 8, 9, 16, 17, 24, 25, 32, 33, 40, 41, and 48-55 have been cancelled. Claims 10-11, 15, 18, 19, 23, 26, 27, 31, 34, 35, 39, 42, 43, and 47 have been withdrawn for non-elected invention. Claims 1-4, 7, 44, and 46 are currently amended. Claims 1-4, 7, 12-14, 20-22, 28-30, 36-38, and 44-46 are pending and under consideration. It is noted that the new species have been added to newly amended claims in order to obviate the rejection under the 112 1st. The newly added species (VCAM-1, MAddCAM-, ICAM-1) and non-elected species (HIF) have not been presented in the previous version of the claims. Because the species are not Harnisch compliant (fail the Harnisch test, see MPEP 803.02) applicant is advised that requirement for restriction or species election may be applied for the CAM species in the amended claims in the future prosecution. Based on the applicant's response to election/restriction filed 1/24/05, only original presented species of CAM along with elected XAA analog is under the consideration currently.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

Priority:

It is acknowledged that the Office has received the certified copy of priority document "NZ336259". Thus, the instant application benefits the date of foreign application, New Zealand, NZ336259.

Rejections Withdrawn

The rejection of claims 1-4, 12-14, 20-22, 28-30, 36-38, and 44-46 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is maintained** is withdrawn in view of applicant's argument.

Art Unit: 1642

Response to Arguments**Rejection under 35 USC § 112 1st paragraph****Drawn to scope enablement**

Claims 1-4, 12-14, 20-22, 28-30, 36-38, and 44-46 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a mammal with advanced or large tumor burdens, or potentiating the activity of T-cell to eradicate an advanced or large tumor comprising the administering B7.1 in combined with DMXAA, does not reasonably provide enablement for the method using any other CAM in combined with any tumor restricted agent is maintained as stated below:

The claims are broadly drawn to a method of treating for a mammal with advanced or large tumor burdens, or for a patient with cancer, or potentiating the activity of T-cell to eradicate an advanced or large tumor comprising the administering any T-cell co-stimulating cell adhesion molecule (CAM) with any tumor growth-restricted agent.

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. The method objective of claims is treating tumor with a CAM plus a tumor restricted agent to effectively eradicating an advanced or large tumor. Thus, it would be expected that one of skill in the art would be able to eradicate an advanced tumor or large tumor without undue experimentation by using the claimed method.

The specification teaches the CAMs in the method include B7.1, B7.2, VCAM-1, MAdCAM-1 and ICAM-1 etc (para 37-40) and the tumor restricted agent in the method include analogs of XAA and FAA, cytokine IL-12, antisense to VEGF, FLT-1 etc (para 50-58). However, the only combined therapy of a CAM and a tumor growth restricting agent used for treating a tumor in the application is administering B7.1 in combination of DMXAA to mice to eradicate tumors (figure 2, 5, 8, 12, paragraph 98). The specification does not provide a method of using any other CAM in combination with any other tumor restricted agent successfully treating or eradicating any large or advanced tumors. The specification does not provide enough direction or guidance for the claimed method of the combination therapy with any CAM combined with any tumor restricted agent encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would use the claimed method without experimentation.

One skilled in the art recognizes that the search for combinations of drugs (each has less effect when it is used alone) exerting a combined effect requires a great deal of empirical testing of agents known to have anti-cancer properties or that may augment an agent having anti-cancer properties (Gerson et al, WO03/070234, page 2, lines 11-14). In addition, not all the analogue of XAA has a tumor restricted function, Futami et al., (J of Immunotherapy, vol 12, 247-255) indicates that 7-methyl-XAA; a analogue of XAA, self, or combination with IL-2 has not synergistic activity in suppression of tumor growth (page 252-253, col 1). Thus, it would be undue experimentation to test two agents in combination in order to determine whether one skilled in the art could use them together for treating a large or advanced tumor.

Since the specification does not provide claimed method for using any other CAM except B7.1 in combination with any other tumor restricted agent except DMXAA, one skilled in the art would not know how to use the claimed method to treat large or advanced tumor comprising administering any CAM combined with any tumor restricted agent.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to claimed method, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention. If Applicants has any objective evidence contrary to the rejection, Applicant is invited to submit it to the Office for reconsideration.

Art Unit: 1642

The response filed 11/22/06 has been carefully considered but is deemed not to be persuasive. Applicant argues *that making and using the invention do not require undue experimentation based on the MPEP 2164.01) and examiner require merely routine experimentation to practice claimed invention (page 10)*. Applicant also states that *the claims have been amended to add more species in order to obviate the rejection (page 11)*. In response to this argument, first, the added tumor restricted agent HIF is not elected species and currently is not under consideration. Second, although the newly added species of CAM, VCAM-1, MAddCAM-, ICAM-1 are stated in the specification and example given for the testing of inhibition of tumor growth alone with the CAMs, none of the species other than B7.1 were tested or shown in combination with DMXAA reagent for the treating large tumor or has ability to eradicate an advance tumor burden as claimed invention. MPEP 2164.01 does state that making and using claimed invention may not need undue experimentation, however, as stated in the rejection above, to satisfy the requirement of 35 U.S.C. 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention, which the factors are described *In re wands*, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988) and those factors are in the consideration for the instant claims. Undue experimentation is required here because the nature of the invention, a method of treating cancer in vivo. If one skilled in the art could not predict the treatment result with any CAM plus DMXAA, if no enough amount of direction or guidance is given by the applicants or in the art, one skilled in the art must perform experimentation or test before practice claimed invention in a mammal with tumor. Instant specification merely provides the evidence that the tumor is not treatable with any CAM alone comprising CAM, VCAM-1, MAddCAM-, ICAM-1 and B7.1. The specification does not provides direction/guidance or any test result that combination of the CAM except B7.1 gene with DMXAA could result in a better treatment for the large tumor than any the reagent alone. Because the nature of the invention and unpredictable treatment result, one skilled in the art would be forced into under experimentation in order to practice the claimed invention. Thus, requirement of 35 U.S.C. 112, 1st paragraph, is not satisfied and applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record.

Art Unit: 1642

Rejection under 35 USC § 103

Claims 1-4, 7, 12-14, 20-22, 28-30, 36-38, and 44-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Futami et al., in view of Olsson et al., as stated below:

The claims are drawn to methods of treating a patient with cancer or potentiating the activity of tumor restricted agent comprising an analogue of Xanthene-4 acetic acid (XAA) or 5, 6 dimethylxanthene-4-acetic acid (DMXAA) for treating cancer by administering T-cell co-stimulatory cell adhesion molecule (CAM) comprising B7.1, CD80 antigen, in conjunction with analogue of XAA.

Futami et al., teach a method of treating tumor by analogues of XAA comprising 5-methyl XAA in conjunction with a T-cell stimulating molecule, IL-2. Futami et al., teach that the activities of XAA analogues can be potentiated by recombinant IL-2 in treating a tumor. Futami et al., teach a method of treating cancer by administering a subject both reagents or administering two reagent at different time (page 249, column 1-2 and page 251, column 1). Futami et al., also teach the analogues of XAA alone or IL-2 alone is not as effective as combined therapy for treating a mice bearing a tumor (figure 2-4).

Futami et al., do not teach that treating cancer with analogue of XAA in conjunction with a CAM.

Olsson et al., teach Human IL-2 is induced by CD80 (B7.1, a CAM molecule) in cancer cells and T cells (entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method to eradicate any advanced or large tumor by administering analogues of XAA in combination of CAM comprising B7.1(CD80) with the expected result for cancer treatment. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to potentiate the activity of single reagent for cancer treatment by a second reagent. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Olsson et al., with the teaching of Futami et al., to treat cancer by administering a patient with a CAM and analogues of XAA comprising DXMAA because Futami et al., have suggested that IL-2 induced by B7.1 and analogues of XAA have a synergy effect for eradicating established tumor when they are administered together and Olsson et al., have shown that IL-2 is induced by a CAM, B7.1. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method by administering CAM and analogues of XAA together, administering one reagent prior to another, or administering additional analogues of XAA for cancer treatment.

Applicants argue in the Remark filed 6/15/06 that the prior art references fail to provide suggestion or motivation to modify the reference or combine the reference teaching. Applicant also argue that there is no teaching or suggestion in either of the references that treatment of XAA and A CAM (B7.1) will produce a synergistic effect in eradicating advance or large tumors. In response to this argument, first, Applicants do not claimed a method of combination therapy has the synergistic effect. Second, although the references do not suggest modification of the method by combining a CAM (B7.1) with analogues of XAA, the method and evidence disclosed by the reference suggests that the agent is replaceable because Olsson et al., have suggested that IL-2 is induced by a CAM, B7.1, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to replace IL-2 with B7.1 in the method taught by Futami et al., for treating tumor. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method by replacing IL-2 with CAM (B7.1) for tumor treatment.

The response filed 11/22/06 has been carefully considered but is deemed not to be persuasive.

Applicant argues first argue that *In no motivation to combine the two references, specifically, Olsson et al., only disclose IL-2 to activate T-cells, never discusses cancer treatment and Futami do not teach or suggest CAM (page 15).* Applicant then argues *the Office failed to provide any evidence to support the prima facie case of obviousness and reasonable expectation of success and combination of the*

Art Unit: 1642

references (page 16) and the combination of references do not teach every limitation (page 17). In response to arguments, first, MPEP 2141.02 states rejection under 35 USC § 103:

In determining the difference between the prior art and the claims, the question under 35 USC103 is not whether the difference themselves would have been obvious, but whether the claimed invention as a whole would have been obvious.

Futami et al., teach a method of treating tumor by analogues of XAA comprising 5-methyl XAA in conjunction with a T-cell stimulating molecule, IL-2 and IL-2 potentates the effect of XAA. Futami et al., also teach that either reagent by itself does not effectively treat established tumor. Although Futami et al., does not teach CAM, B7.1, Olsson et al., teach Human IL-2 is induced by CD80 (B7.1) in cancer cells and T cells, which indicate that CD80 (B7.1)'s action on eradication of tumor is through induction of IL-2 and activation of T-cell by IL-2 for killing tumor cells. Therefore, replaced IL-2 with its stimulator B7.1 would result in same treatment effect and one skilled in the art would be motivated to reach the claimed invention with reasonable expectation of success by replace IL-2 with B7.1 in the treatment method. Thus, the claimed invention as whole would have been obvious over the art in combination under 35 U.S.C 103 and combined references teach every limitations of claimed invention.

Applicant further arguer *neither Futami nor Olsson teach or suggest the treatment of advanced or large tumor. Futami injected tumor and treated only 7 days after tumor injection, while the present invention is focused on extremely large tumor of 0.6-0.9 cm (page 18).* In response to this argument, although the tumor size after 7-day inoculation of tumor cells is not explicitly described in the reference, one skilled in the art would know injection of 10^5 tumor cells would result in formation of tumor colonies and certain size of the tumor 7 days after injection. *Futami et al., did state the tumor regression was achieved after treatment (page 254, col 1), which indicates the tumor being formed and regressed after treatment. Moreover, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to optimize the treatment method according to the growth rate and condition of different tumors established in the mice comprising the tumor size and day or dose of the administration in order to get better result and response because Futami et al., has suggested the treatment method, material used in the method, and method steps. Thus, claimed invention as whole would have been*

Art Unit: 1642

obvious over the art in combination and combined references suggest all the limitations of claimed invention.

Thus, Applicant's argument has not been found persuasive and the rejection is maintained for the reason of record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.


Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY


SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

